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"WHAT IS THE PROBABILITY THAT RADIATION CAUSED A PARTICULAR CANCER?"

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ABSTRACT

Courts, lawyers, health physicists, physicians, and others are searching for a credible answer to the question posed in the title of this paper. The cases in which the question arises frequently stem from an individual that has cancer and they, or their next-of kin, are convinced that a past radiation exposure--usually small--is responsible for causing it.

An arithmetic expression of this problem is simple: the probability of causation by the radiation dose in question is equal to the risk of cancer from the radiation dose divided by the risk of cancer from all causes. The application of risk factors to this equation is not so simple. It must involve careful evaluation of the reliability of and variations in risk coefficients for development of cancer due to radiation exposure, other carcinogenic agents, and "natural" causes for the particular individual. Examination of our knowledge of these various factors indicates that a large range in the answers can result due to the variability and imprecision of the data. Nevertheless, the attempts to calculate a the probability that radiation caused the cancer is extremely useful to provide a gross perspective on the probability of causation. It will likely rule in or out a significant number of cases despite the limitations in our understandings of the etiology of cancer and the risks from various factors. For the remaining cases, a thoughtful and educated judgment based on selected data and circumstances of the case will also be needed before the expert can develop and support his opinion.

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Introduction

The question in the title of this paper is a subject of immense interest today. More cases are finding their way into the courtrooms of our country each year for a legal decision on questions of whether ionizing radiation is a causative agent of health effects in former radiation workers or, in some special cases, even members of the general public. Cancer is the most likely disease for which the question arises.

The word cancer is a layman's term to describe a growth or tumor that is characterized by potentially unlimited growth of cells with local expansion by invasion of neighboring tissues and systemic spread by metastasis. There are many different types of cancer; each type can be identified by recognition of basic cell features that are characteristics of the tissue or organ from which the cancer arose. Therefore, most cancers can be identified as to type. We do not know exactly how the control of cell reproduction and growth gets changed to produce a cancer. We know cancer is not a single disease and can be caused by a variety of circumstances and agents, including genetic heritage, age, immunological deficiencies, and exposure to physical and chemical agents. It is not possible to identify the cause of a particular cancer by any diagnostic test; a specific type of cancer appears to be the same disease regardless of cause. A legal determinaion of the cause of a cancer is addressed by a series of expert witnesses reviewing the facts and presenting an opinion. The expert opinion is, hopefully, based on present knowledge, but it is readily apparent that the expert opinions are highly variable and diametrically opposite opinions are frequently forthcoming.

The purpose of this paper is to discuss a method that expresses the radiation dose and associated cancer risk in terms of probabilities. This type of determination, while it may possibly enter into the opinion of an expert witness, is not commonly used in legal cases as a numerical determination. Such a probability calculation could be used as a principal determinant as to whether radiation was "more likely than not" to have caused the disease. Could such a determination reduce the time and costs involved in litigation of these cases? Is there enough information available that this type of method can provide useful answers to the question? Will the courts or hearing boards accept a more mathematical, dare we say objective, method for arriving at an answer?

Obviously the latter question cannot be answered until one develops and examines the idea that a calculated probability is desirable and more reliable than the existing system. In fact, such development and evaluation is going on now by a committee of the National Council on Radiation Protection under the chairmanship of Dr. Victor Bond. Until their report becomes available, it behooves us to become aware of some basic ideas for deriving probabilities in this type of question and to start thinking about the limitations and strengths of this method. Those called upon to address questions on the "probability of causation" of cancer after radiation exposure should apply these calculational techniques to gain experience in this application. Discussion on the practical application of this concept to cancer risk attributable to radiation exposure has been presented by Bond.[1]

The basic principle of calculating probability of causation is deceptively simple. One takes the risk of cancer per year for the radiation doses in question and divides by the total risk of cancer per year for the particular individual. Thus, we are dealing with two risk terms: (1) risk of cancer induction after radiation, and (2) the total risk of cancer induction in the individual. In this paper I would like to explore, in a preliminary way, our knowledge about these two terms. Let us start with the numerator -- the risk of cancer after a radiation dose(s).

The Numerator -- Risk of Cancer After Radiation Dose

This meeting focuses on the epidemiologic methods and studies used to estimate the risk of inducing excess cancers in groups of people exposed to ionizing radiation. The result is usually expressed as the number of excess cancers produced per million persons per rad. This is called an absolute risk coefficient since it describes a specific number of excess cancers per million persons per rad. The number may be the lifetime risk or an annual risk. This risk is considered to be independent of the risk from other causes of cancer. The current risk estimates commonly used are those of the National Academy of Sciences' BEIR III[2] report or the United Nation's Scientific Committee on the Effects of Atomic Radiation.[3]

Unfortunately, no one knows how reliable these risk estimates are. They are derived from epidemiologic studies of human populations exposed mostly to doses of 10 to 100 rem or above. The doses were mostly delivered at high dose rates. In most legal cases, the radiation doses are low and delivered at low dose rates. The dose-response curves are not known for these types of exposures and some assumptions must be made. Key assumptions for the linear model commonly used are that the risk is strictly proportional to the dose, independent of the dose rate, and vanishes only when the dose is zero.

One of the controversial issues at hearings, of course, is what risk coefficients are most reliable and credible. Each expert can develop his or her own risk numbers and try to convince the court that someone else's is wrong. Hopefully, in time, data from epidemiologic studies will confirm or modify risk coefficients so that there are fewer discrepancies of major proportions such as are now being heard at each case hearing. The risk coefficients from the references described above are the best available, and it seems doubtful that one could make better subjective judgments than to use risk estimates as carefully reviewed as these. Application of any methodology, such as calculation of the probability of causation, must not hamper the revision of risk coefficients as better data become available.

There are other questions of importance in determining radiation risk. The radiation dose is perhaps the most important. In cases of cancer, we wish to know the dose to the tissue of cancer origin not the dose to the personnel dosimeter. It is important to note that internal emitters are frequently involved in these cases. For purposes of calculating a total dose to the organ of interest, it is necessary to add the internal and external doses. The problem of assuming reasonable dose distribution within the body is one of the more difficult areas for both internal and external doses. No system for determining probable causation can counterbalance such potential errors. One can only use the best available data and be aware of potential deficiencies.

Despite these problem areas, the ultimate question is whether errors in estimating dose and risk are any worse for calculating a probability of causation or for testifying on a more subjective basis.

The Denominator -- Total Cancer Risk of the Individual

The total cancer risk of an individual is complex and dynamic. A way of estimating total risk is to start with the known incidence of specific cancers in a population. Risk modifiers peculiar to the individual in question may be applied to this baseline incidence. For a single exposure to radiation, the calculation of Probability of Causation (P.C.) is as follows.

$$P.\ C. \quad = \frac{D \times C}{B + M + (D \times C)} \qquad (1)$$

Where D is the organ dose in rads (rems), C is the radiation risk coefficient appropriate to the kind of cancer and age at exposure, B is the baseline rate for that cancer at the age when the cancer was detected, and M is any known modifying factor in this individual that may be expected to change the baseline incidence significantly.

For multiple radiation exposures, the formula becomes

$$P.\ C. \quad = \frac{D_1C_1 + D_2C_2 \ldots D_xC_x}{B + M + D_1C_1 + D_2C_2 \ldots D_xC_x} \qquad (2)$$

The baseline incidence rates for specific cancers in the United States are available in the report of the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute.[4] This report presents incidence and mortality data from 1973 - 1977 for ten areas in the United States, plus Puerto Rico. It has the data on cancers, classified by type, for age, sex, color, and region.

Figure 1 shows the changing rate of cancer incidence with age. The rate increases rapidly after about 40 years of age. The incidence rates used for calculating probability must be appropriate for the sex and age of the individual. Ethnicity is another important parameter and rates for the appropriate group should be used if possible. Rates in different geographical areas may also be different by a factor of 2 or 3 in some instances.

Within the population from which the baseline cancer incidence rate is derived are present all effects from exposure experiences normal to the population. Background radiation and average medical radiation exposures will be present in the rates. Thus no correction is needed unless other exceptional exposures are known to have occurred.

These data, therefore, give reasonable values for baseline incidence, but they are average rates and are not necessarily appropriate for all situations. This is the reason for the modifying factor, M.

Smoking is known to cause increased risk of lung cancer. In some cases it will be appropriate to adjust for this difference. Lung cancer in nonsmokers is likewise less than the SEER incidence rates, which include smokers in the data.

Family history of cancer is another factor that may cause one to adjust the baseline cancer incidence rate in a few special situations. For example, the breast cancer risk increases about 9 fold in a female whose mother had a history of bilateral breast cancer at premenopausal age.[5] In fact, for such an individual the probability of getting breast cancer is greater than 50 percent as a result of their familial predisposition.

Another modifying factor is a history of other exposures to carcinogens. These most often will appear in an occupational history. Here too the appropriate risk value will be most difficult to quantify. In general, these cancer risk values are less well known than for ionizing radiation.

The manner in which one might modify baseline incidence for some of the special risks just given as illustrations is a serious problem. Cancer risk from carcinogens, genetic heritage, and other potential modifiers are not well characterized. Data available to modify baseline incidence to account for such variables is often not available. In general, it seems advisable to me not to modify baseline incidence unless the special variable for the individual exerts an especially strong known effect, such as factors of 3 or more, and then modification must be done cautiously.

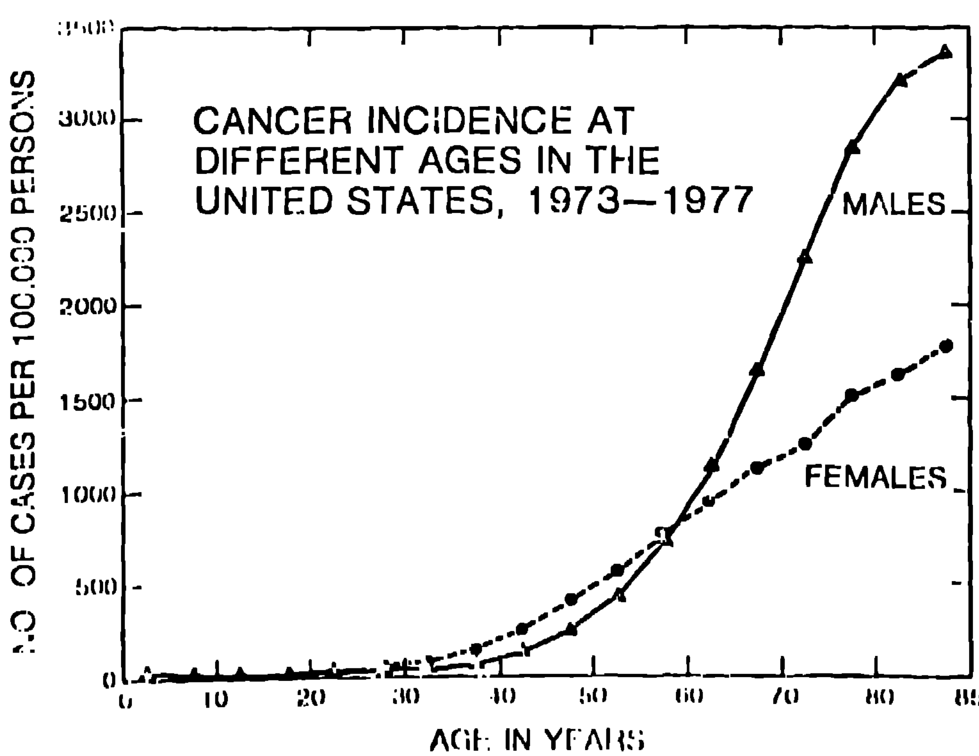

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Figure 1

Discussion

A brief description of potential sources of error in estimating the cancer risk after radiation, dose calculations, baseline incidence rates, and other less well-defined cancer risks may make one nervous on the use of a calculated probability of causation. One must remember, however, that the method demands several important requirements. The risk we are calculating is for a person who has developed cancer. This is not attributable risk for future cancers, but applies only for an individual who already has the disease. The cancer must be one that is recognized as being induced potentially by radiation as shown in the risk coefficients. Further, the time relationships between radiation exposure and the subsequent cancer diagnosis must be in concert with our knowledge of radiation effects. Thus, the latent period for many cancers is expected to be about 10 years, while for leukemia and bone cancers a latent period of only two years would be more appropriate. The risk of excess cases of leukemia appears to be gone by 25 or 30 years after radiation exposure; thus, this limitation on time since exposure would also be applied before calculating the likelihood that the leukemia resulted from a particular radiation exposure.

Inspection of a table of calculated probabilities of causation leads one to appreciate the marked differences that are present for the same radiation exposure at different ages. This is due primarily because of the marked differences in the incidence rates for the different types of cancer and at various ages and also different risk coefficients for specific cancers after radiation.

As an example, look at the risk of developing leukemia from radiation doses. Table I lists the absolute risk coefficients from the BEIR - III report when exposure to a male occurs at ages 20, 40, and 60. The risk per year at age 60 is about twice that at the earlier ages. Table II shows the baseline incidence rate of leukemia not including chronic lymphocytic leukemia, which is not produced by radiation. The incidence of leukemia in a 65 year old white male is over eight times that at age 25.

TABLE I

ABSOLUTE RISK COEFFICIENTS

Cases Per Person-Years Per Rad (Specific Organ Dose)

Example: Risk of Leukemia in White Males
Per Rad to Bone Marrow

Age	BEIR-III Risk (Risk/10^6)
20	2.5
40	1.9
60	4.3

TABLE II

BASELINE INCIDENCE

New Cases of Cancer Per Million Persons Per Year

Example: Leukemia (less chronic lymphocytic type) in white males

Age	Incidence (Cases/10^6)
25	28
45	69
55	234

Now let us suppose a white male is exposed to 1 rad of penetrating x-ray diation to his bone marrow at age 20. This might be equivalent to a recorded dose 2 rad on a personnel dosimeter at the surface. The man develops a leukemia at e 25. What is the probability that his leukemia was caused by the radiation? ble III shows the calculation of a probability of 8.2%. This suggests there is t a high probability that the radiation caused his disease.

Table IV shows calculated probabilities of causation that a leukemia, other an chronic lymphocytic type, may have resulted from a 10 rad dose to the bone rrow at ages 20, 40, and 60. In each case, the individual is assumed to have veloped leukemia five years after exposure. No modifiers are applied to the seline incidence. The probability of causation is about 3 times higher for the 25 ar old (47%) as for the 65 year old (16%). Note the major effect of the baseline cidence in reducing the likelihood that the disease was caused by the radiation se at the older ages.

TABLE III

PROBABILITY OF CAUSATION

Percent Probability of Cancer
from Radiation Risk
Compared to Total Cancer Risk

Example: Leukemia, other than chronic lymphocytic, in white male occurs 5 years after 1 rad bone marrow dose at age 20

$$\frac{\text{Rad Dose x Risk Coefficient}}{\text{eline Incidence + (Rad Dose x Risk Coefficient)}} = \frac{1 \times 2.5}{28 + (1 \times 2.5)} \times 100 = 8.2\%$$

TABLE IV

VARIABILITY OF PROBABILITY OF CAUSATION (P.C.) WITH AGE

Example: Leukemia in White Male 5 Years After 10 Rad Dose

ge	Baseline Incidence/10^6	Radiation Risk/10^6	Total Risk/10^6	%P.C.
25	28	25	53	47%
45	69	19	88	22%
65	234	43	277	16%

The question remains as to the possible application of such calculations as a ·ocedure to improve the manner in which we attempt to determine causation of ancers that occur after a radiation exposure. The calculation requires the use of iltiple factors, each of which can be an item for argumentation. One possible dvantage of calculating P.C.'s is that the procedure helps focus attention to the ieces of information required for such determination. Presumably formal ecognition of the value in such calculations will bring added attention to the eed for information to provide better estimates.

The calculation of a probability of causation could seemingly be used in a uple of ways. The first would be as a basis for an opinion by an expert in his stimony. It is a proper method for evaluating and establishing an opinion on the estion of causation. Thus far, lawyers and courts have had a reluctance to use is type of methodology. The use of subjective expert opinion often seems more fective. If there is any radiation dose involved in the case, a calculation of is sort will always produce a positive number as the probability of causation. nce it is not clear what the jury or judge may do with such probability, no tter how small, it apparently is safer not to introduce the calculation at all, st the opinion.

A second type of use for such a calculation is the possibility that it could used as part of an administrative procedure for evaluation of probability of usation. This seems particularly appropriate, or possible, with cases involving rkman's compensation or occupational disease. With legislative authority, it uld seem possible that an administrative determination on the probability of usation could be successful in formulating a reasonable answer quickly and onomically. The administrative procedure would proceed by gathering the cessary information on the case, deriving a probability of causation, and using cepted schedules of settlement similar to current workman's compensation hedules for permanent disabilities.

One important result of litigation is the careful review of the history and posure record of the involved individual. Any administrative procedure must not duce the scrutiny of the details of the case that is needed for protection of th sides of the case. All the elements of a "probability of causation" calculation are suitable subjects for such careful review. These include radiation dose, radiation risk coefficients, baseline incidence, and other risk factors. Such review of the values used in the calculation might be more pertinent than the current method of evaluating a more subjective expert witness statement.

It is likely that a review of many cancers alleged to be caused by radiation will fall into either high or low values of probability of causation, for example, below 10 percent or above 50 percent. As an administrative procedure, it appears that a calculation of probability, along with careful review of the appropriate values to be used, would serve well in determining the likely association of the cancer and a radiation dose. The relatively smaller number of cases falling in the intermediate range, say 10 to 50 percent, may be appropriate subjects for additional review. It is apparent that some form of appeal mechanism must be available to all parties regardless of the calculational results.

Review of the effect of this type of methodology on liability of employers is already being performed. Catlin and Parmentier[6] point out that the probability of causation method is shown to be quite sensitive to input parameter selection. Furthermore, the liability impact is highly influenced by the level of probability established by law as the floor for compensation of cancer cases. By interpretation of such legal language as "more likely than not," one might assume the law would use 50 percent probability as the level of liability. Only time will tell if such an assumption is correct.

In my opinion, further review of this question is likely to show that calculation of probability of causation will address the question of association of radiation and cancer in an efficient and effective manner for a majority of cases. Areas of discussion or argumentation on the calculation will occur on the selection of appropriate parameters to use and will serve to focus on the most important factors for determining causation. Even in these instances, the procedure will be performing a useful function. Furthermore, the need for better data on some of these parameters will become apparent, if not already known, and future determinations will improve as the necessary research and experience is obtained.

<u>Conclusion</u>

Calculation of the probability that cancer in an individual is caused by radiation is limited in its accuracy by our knowledge on the overall causes of cancer. Cancer risk from radiation is better known than for other carcinogens. Cases of cancer alleged to be due to radiation are currently decided by expert testimony that may not reflect accurately the complex relationship of radiation risk, baseline incidence of cancer, age, and other risks. Application of a calculation of probability of causation, despite current limitations, does focus considerations on those factors that bear most directly on the question. It seems reasonable that many cases could be resolved by an administrative procedure for workman's compensation law if the probability of causation is above or below certain limits, perhaps above 50 percent probability or below 10 percent. On intermediate values a thoughtful and educated judgment by the expert based on the specific data and circumstances of the cases will also be needed to develop and support his final opinion.

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